

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 11

R E M A R K S

A. Summary of the Invention

Broadly, in a first aspect, the invention of the subject application as amended relates to a method for determining the genotype of a subject at a genetic locus within genetic material obtained from a biological sample from the subject. The method comprises a step of reacting the material at the locus to produce a first reaction value indicative of the presence of a given allele at the locus. A data set is formed which includes at least the first reaction value. The method of the invention further comprises a step of establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of the invention also includes a step of applying the first reaction value to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. Finally, in such first aspect, the method of the invention comprises a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution to determine a measure of the conditional probability of each genotype of interest at the locus.

In a second aspect, the invention of the subject application as amended relates broadly to a method of associating with a sample of genetic material from a subject (i) one of a predetermined plurality of genotypic classes defined with respect to a genetic locus sited in the genetic material and (ii) a confidence measure for the association of the genotypic class with the sample. Each genotypic class identifies either a possible genotype for the subject defined with respect to the genetic locus or a failed-experiment condition. Each genotype is defined by the identity of one or more alleles defined with respect to the genetic locus.

In such second aspect of the invention, the method of the invention comprises the step of carrying out one or more allele-sensitive reactions on the genetic material of the sample at the genetic locus to obtain a least two quantitative allele-indicative reaction values. Each allele-

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 12

indicative reaction value is indicative of the likely presence or absence of a particular allele defined with respect to the genetic locus. The reaction values corresponding to the sample are processed to form a reaction-value data point.

With respect to such second aspect, the method of the invention includes a further step of associating one of the genotypic classes with the sample using the reaction-value data point corresponding to the sample to define a sample genotypic class. The method also includes the step of obtaining with respect to each of the genotypic classes corresponding reaction-value data-point conditional-probability-measure distribution information which provides, over a set of hypothetical reaction-value data points, a conditional probability measure as a function of the hypothetical reaction-value data point given the genotypic class.

Regarding such second aspect of the invention, the method of the invention further includes the step of evaluating the reaction-value data-point conditional-probability-measure distribution information corresponding to the genotypic class associated with the sample with respect to the reaction-value data point corresponding to the sample to obtain a reaction-value data-point conditional probability measure of the reaction-value data point given the sample genotypic class.

Finally, in such second aspect, the invention of the application as amended includes the step of establishing a confidence measure for the association of the sample genotypic class with the sample using the reaction-value data-point conditional probability measure of the reaction-value data point given the sample genotypic class.

B. Summary of the Outstanding
Office Action

In the Office Action of 18 March 2005, claims 75 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 96 through 98 inclusive, 102, 106 through 109 inclusive, and 112 through 115 inclusive were rejected under 35 U.S.C. §103(a) as unpatentable over a publication

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 13

by Kimpton *et al.* in *PCR Methods and Applications*, volume 3, pages 13 through 22 (August 1993) (“the Kimpton *et al.* publication”) in view of a publication by Ledwina *et al.* in *Biometrics*, volume 36, pages 160 through 165 (1980) (“the Ledwina *et al.* publication”) and further as motivated in view of a publication by Jeanpierre in the *Annals of Human Genetics*, volume 56, page 325 through 330 (1992) (“the Jeanpierre publication”). It was asserted that the Kimpton *et al.* publication disclosed at page 14 a method of determining the genotype at a locus within genetic material obtained by PCR amplification. With citations to page 14, columns 1 through 3 of the Kimpton *et al.* publication, it was asserted that a method of the publication included reacting material at the locus to produce a first reaction value. It was asserted further, with a citation to pages 14 through 16 of the Kimpton *et al.* publication, that the publication disclosed forming a data set including the first reaction value by assembling reaction value data points for samples with each reaction value data point assertedly corresponding to a respective one of the samples and including at least one reaction value. It was asserted that the data points represented by each of the separate peaks in Figure 1 represented a different sample and were assembled in Figure 2. With a reference to pages 16 and 17 of the Kimpton *et al.* publication, it was asserted that the publication disclosed determining the genotype and a confidence score for each reaction value data point assertedly to determine the genotype and confidence score at the genetic locus for each sample. It was asserted that Table 2 on page 17 of the publication provided for each reaction point the genotype and a standard deviation based on the data obtained from a “step d,” which step d appeared not to be further identified in the Office Action. With regard to claims 77 and 78, it was asserted in the outstanding Office Action that the Kimpton *et al.* publication disclosed reacting the material at multiple loci at page 14, Table 1. With regard to claims 80 through 82, 114, and 115, it was asserted that the Kimpton *et al.* publication on page 17 disclosed multiple alleles in probability distributions; however, such probability distributions appeared not to be identified further in the Office Action. Table 2 was cited with the assertion that the Table disclosed that the method of the publication was applicable to any number of alleles. It was asserted in the outstanding Office Action that the Kimpton *et al.* publication expressly disclosed

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 14

the use of multiple data points derived from multiple runs of an automated apparatus including multiple data sets in the method and apparatus disclosed at page 16 and in Figure 2.

Significantly, it was admitted in the outstanding Office Action that, although the Kimpton *et al.* publication disclosed the use of a Hardy-Weinberg test, the publication did not disclose establishing a distribution set of probability distributions and did not disclose applying the reaction value of the distributions to determine a measure of the conditional probability of each genotype of interest at the locus. It is respectfully submitted that it does not appear possible to square the admission in the outstanding Office Action that the Kimpton *et al.* publication did not disclose establishing a distribution set of probability distributions with the assertion in the Office Action with respect to claims 80 through 82, 114, and 115 that the publication considered multiple alleles in probability distributions.

It was asserted in the Office Action of 18 March 2005 that the Ledwina *et al.* publication disclosed a method in which genotypes could be determined in which the Hardy-Weinberg test was modified assertedly to include the steps of establishing a distribution set of probability distributions and associating hypothetical values of a variable not identified in the Office Action with corresponding probabilities for each genotype of interest. Pages 162 and 163 of the Ledwina *et al.* publication were cited in this regard. It was asserted further that the Ledwina *et al.* publication disclosed the step of applying an unspecified first value to each pertinent probability distribution to determine a measure of conditional probabilities of each genotype of interest, citing in particular pages 162 and 163 of the Ledwina *et al.* publication. It was asserted further in the Office Action on 18 March 2005 that, with respect to claims 76 and 79, the Ledwina *et al.* publication, in referring on page 162 to “conditional probability distribution of (T,Z) is multinomial with $\frac{1}{2}m(m+1)$ cells and with the vector of cell probabilities $g=(g\dots)$,” assertedly disclosed a plurality of distributions which were hypothetical.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 15

It was asserted in the outstanding Office Action that the Jeanpierre publication motivated the use of computation of unknown genotypes to analyze conditional probabilities relative to a distribution of hypothetical reaction values. Page 330 of the Jeanpierre publication was cited in this connection.

It was asserted in the outstanding Office Action that it would have been *prima-facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of the Kimpton *et al.* publication to use a conditional probability distribution method assertedly disclosed in the Ledwina *et al.* publication, since the Kimpton *et al.* publication assertedly noted that the analysis of the publication used Hardy-Weinberg equilibria and since the Ledwina *et al.* publication disclosed a class of admissible tests for the Hardy-Weinberg equilibrium in a multiple allelic system. It was asserted that an ordinary practitioner would have been motivated to apply the asserted hypothetical distribution analysis to genotyping since the Jeanpierre publication assertedly disclosed certain gains from creating such a distribution, including avoiding a hazard of incorrectly using a simple average of conditional probabilities instead of a harmonic mean.

In the Office Action of 18 March 2005, claims 75 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, 100, 102, and 106 through 115 inclusive were rejected under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as motivated in view of the Jeanpierre publication, and further in view of published International Patent Application WO 92/15712 to Goelet *et al.* (“the Goelet *et al.* ‘712 published international application”). It was noted that the Goelet *et al.* ‘712 published international application disclosed genetic bit analysis methods. It was asserted in the Office Action that it would have been *prima facie* obvious to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of a publication by Clark in *Mol. Biol. Evol.*, volume 7, pages 111 through 122 (March 1990) (“the Clark publication”) with the use of the genetic bit analysis or allele specific amplification to develop the data, in view of a statement

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 16

in the Goelet *et al.* published application on page 8, lines 27 through 33. It was asserted that an ordinary practitioner would have been motivated to substitute the genetic bit analysis method for PCR amplification in order to minimize the need for gel electrophoresis and enhance the automatability of the process to speed analysis and minimize costs as assertedly motivated by the Goelet *et al.* '712 published international application.

With reference to comments in a reply to an office action filed on 2 October 2003 regarding a previous claim rejection citing the Ledwina *et al.* publication, it was asserted in the Office Action of 18 March 2005 that specific motivation had been provided in the rejection to combine the cited art. It was asserted further that the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication were in the same field of endeavor, that of genetic analysis, and that, in such assertedly narrow field, each of the publications was pertinent to the problem of analysis of genotypes. Without reference to specific passages in the cited publications, it was asserted in the outstanding Office Action that a hypothetical ordinary practitioner, assertedly needing mathematical tools to analyze genotypes, would look to other papers involved in the analysis of genotypes to identify statistical tools which worked best. It was asserted that such hypothetical practitioner using the analytical method of the Kimpton *et al.* publication would assertedly have been motivated by the Jeanpierre publication to use conditional probabilities assertedly to more accurately determine genotypes which assertedly would have further motivated the practitioner to look at the Ledwina *et al.* publication assertedly for teachings concerning how to apply conditional probabilities to the method of the Kimpton *et al.* publication assertedly in order to improve the accuracy of genotype determination.

C. Summary of the Present Amendments
And Request for Reconsideration

In the present response, the respective preambles of independent claims 75, 96, and 106 have been amended. The preamble of independent claim 75, for example, has been amended to refer to “[a] method of determining the genotype of a subject at a locus within genetic material

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 17

obtained from a biological sample from the subject.” Generally parallel amendments have been made to the respective preambles of independent claims 96 and 106. The amendments to claims 75, 96, and 106 find support in the application as originally filed, for example, at page 4, line 28 through page 5, line 3 and page 5, lines 19 through 21. It is submitted therefore that the amendments to claims 75, 96, and 106 do not constitute new matter.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. Summary of Interview with Examiner

The attorneys for the applicants hereby make of record a telephonic interview with respect to the subject application courteously granted by Examiner Jeffrey N. Fredman to the undersigned attorney on 26 July 2005.

Prior to the interview, a draft copy of the amendments to claims 75, 96, and 106 set out above and a copy of an excerpt from the book *An Introduction to Genetic Analysis, Fifth Edition*, by Griffiths *et al.* (W. H. Freeman, 1993); specifically, pages 750 through 752; (“the Griffiths *et al.* book excerpt”) were sent to Examiner Fredman on 13 July 2005 by telefacsimile. The Griffiths *et al.* book excerpt had been cited in an information disclosure statement submitted to the Patent and Trademark Office on the previous day, 12 July 2005.

In the interview on 26 July 2005, the disclosures of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication were discussed generally with regard to the subject matter of rejected independent claims 75, 96, and 106 of the subject application. In particular, the concept of Hardy-Weinberg equilibrium in the context of the disclosures of the Kimpton *et al.* publication and the Ledwina *et al.* publication was discussed.

No agreement was reached with respect to any of the claims of the application in the interview.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 18

E. The Rejections Under 35 U.S.C. § 103(a)

E.1 The Kimpton *et al.* Publication in View of
the Ledwina *et al.* Publication as Motivated
in View of the Jeanpierre Publication

It was admitted in the next-to-last paragraph on page 6 of the Office Action of 18 March 2005 that the Kimpton *et al.* publication, the principal citation relied on in the Office Action, did not disclose establishing a distribution set of probability distributions. The Kimpton *et al.* publication did not therefore disclose determining a measure of a conditional probability of each genotype of interest at a locus by applying reaction values to the distribution, as apparently also admitted in the next-to-last paragraph on page 6 of the Office Action. The attorneys for the applicants fully agree with the analysis of the Kimpton *et al.* publication in the paragraph under discussion on page 6 of the Office Action to the effect that the Kimpton *et al.* publication would not have disclosed the establishment of a distribution set of probability distributions and submit in addition that the Ledwina *et al.* publication does not cure the admitted infirmities of the Kimpton *et al.* publication as a reference against claims 75 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 96 through 98 inclusive, 102, 106 through 109 inclusive, and 112 through 115 inclusive as amended, for the reasons discussed below.

The Kimpton *et al.* publication disclosed automated DNA profiling, based on detection of amplified tri-, tetra-, and pentanucleotide short-tandem-repeat (“STR”) loci by electrophoresis on denaturing polyacrylamide sequencing gels using automated fluorescence-based technology. According to the abstract of the Kimpton *et al.* publication, the system of the publication used an internal size standard in each sample to permit the short-tandem-repeat products amplified by PCR to be sized automatically. In the method of the Kimpton *et al.* publication, three multiplex short-tandem-repeat systems containing a total of fourteen different loci were used, with different fluorescent markers used for loci which had overlapping allele size ranges.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 19

According to page 13, column 3, lines 13 through 19 of the Kimpton *et al.* publication, the ability to resolve PCR products differing in size by just one base allowed precise allele designation for short-tandem-repeat loci. However, the Kimpton *et al.* publication disclosed that, with respect to amplified dinucleotide short-tandem-repeat products, the amplification process gave rise to artifactual “stutter” bands which complicated allele designation. According to the Kimpton *et al.* publication at page 13, column 3, lines 13 through 29, the complication of artifactual stutter bands could be avoided by using short-tandem-repeat loci with tri- and tetrameric repeats which had wider allele spacings than short-tandem-repeat loci with dinucleotide repeats. In the words of the Kimpton *et al.* publication:

[T]he ability to resolve PCR products differing in size by just 1 base on polyacrylamide gels allows precise allele designation, thus eliminating the need for continuous allele distribution models currently employed with VNTR systems.

Analysis of dinucleotide STRs has revealed enzyme slippage during amplification, resulting in artifactual “stutter” bands. This makes unambiguous allele designation difficult. However, tri- and tetrameric repeats, which have a wider allele spacing, appear to be significantly less prone to slippage and are therefore more suitable for individual identification. [Footnotes omitted.]

The above quotation from the Kimpton *et al.* publication regarding the choice of short-tandem-repeat loci with tri- and tetrameric repeats is significant with respect to the rejections relying on the Kimpton *et al.* publication in the Office Action of 18 March 2005 in that, it is respectfully submitted, the quotation refutes the assertion in the Office Action that an ordinary practitioner using the analytical method disclosed in the Kimpton *et al.* publication would have been motivated to look for statistical methods to determine genotypes more accurately. In the analytical method disclosed in the Kimpton *et al.* publication, short-tandem-repeat loci were deliberately selected in order to permit unambiguous allele designation using polyacrylamide gels and with a view to eliminating any need for continuous allele distribution models. A practitioner purporting to use the analytical method disclosed in the Kimpton *et al.* publication who looked for statistical methods to determine genotypes more accurately, as hypothesized in the Office

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 20

Action of 18 March 2005, would have been going against the plain disclosure of the publication read as a whole.

The Court of Appeals for the Federal Circuit has held that in analyzing the differences between a claimed invention and the disclosure of a prior-art reference pursuant to 35 U.S.C. § 103, the prior-art disclosure must be considered in its entirety, including portions that argue against obviousness. *Bausch & Lomb v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 420 (Fed. Cir. 1986). The court in *Bausch & Lomb* quoted with approval an earlier decision by the Court of Customs and Patent Appeals, which held:

It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.

In re Wesslau, 147 USPQ 391, 393 (CCPA 1965). To fail to consider a prior-art disclosure in its entirety, including portions that argue against obviousness, constitutes improper hindsight analysis according to the court in *Bausch & Lomb*.

With respect to the Kimpton *et al.* publication, it is submitted that the publication did not merely fail to disclose establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at a locus within genetic material in connection with a method involving determining the genotype of a subject at the locus using a reaction value indicative of a given allele at the locus, but, read as a whole as required under applicable appellate-court precedent noted above, would have affirmatively led persons of ordinary skill in the art away from use of probability distributions in connection with such a genotype-determination method. To ignore the disclosure of the Kimpton *et al.* publication that short-tandem-repeat loci for the genotype-determination method of the publication be particularly selected in order to permit unambiguous allele designation using

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 21

polyacrylamide gels and with a view to eliminating any need for continuous allele distribution models would be, it is submitted, to engage in impermissible hindsight analysis.

Concerning the technique for automatically sizing the short-tandem-repeat products in the procedure of the Kimpton *et al.* publication, the publication disclosed at page 16, column 1, lines 9 through 18 that amplification products of the short-tandem-repeat loci were tagged by the attachment of a fluorescent dye molecule to one of each pair of the locus-specific amplification primers. Amplification products from each of the three multiplex amplification-reaction systems, each together with a dye-labeled internal lane standard, were respectively electrophoresed for eight hours on a polyacrylamide denaturing sequencing gel in an automated DNA sequencer. See page 15, column 1, lines 17 through 25 of the publication. During electrophoresis on the denaturing polyacrylamide gels, amplified products were detected by laser scanning. According to column 1, lines 17 through 34 of page 15 of the Kimpton *et al.* publication, fragment sizes after electrophoresis on the automated DNA sequencer were determined using software employing a method of second order regression to establish a curve of best fit for the internal standard in each lane. According to column 3, lines 42 through 46 of page 19 of the publication, the software sized PCR products automatically against the internal ladder standard. Other than the reference to second order regression, internal operation of the software for determining fragment sizes against an internal lane standard does not appear to be described in the Kimpton *et al.* publication.

It was disclosed at page 16, column 1, line 51 through column 2, line 15 of the Kimpton *et al.* publication that for twelve of the fourteen short-tandem-repeat loci, the maximum band-size range was sufficiently small relative to the minimum repeat-unit size to permit unambiguous allele designation. For the remaining two loci, according to page 16, column 2, line 16 through column 3, line 14 and page 19, column 3, line 56 through page 20, column 1, line 4 of the publication, variability between polyacrylamide gels did not allow reliable allele designation even though differences between allele bands were readily resolvable on the gels. Allele

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 22

designation could be accomplished for the two loci in question according to the publication by running an allelic ladder on each gel for the two loci. As noted above, the attorneys for the applicants agree with the assessment in the next-to-last paragraph on page 6 of the Office Action of 18 March 2005 that the Kimpton *et al.* publication did not disclose establishing a distribution set of probability distributions and applying a reaction value to the distributions to determine a measure of a conditional probability of each genotype of interest at the genetic locus under investigation. Indeed, the attorneys for the applicants submit further that, for the reasons discussed above, the Kimpton *et al.* publication not only failed to disclose establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at a locus within genetic material in connection with a method involving determining the genotype of a subject at the locus using a reaction value indicative of a given allele at the locus, but would have affirmatively led persons of ordinary skill in the art away from use of probability distributions in connection with such a genotype-determination method.

In contrast, independent claim 75 of the subject application as amended is directed to a method for determining the genotype of a subject at a genetic locus within genetic material obtained from a biological sample from the subject which includes a step, among others, of establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of amended claim 75 further includes a step of applying a first reaction value indicative of the presence of a given allele at the locus to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. The method of claim 75 as amended also includes a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution.

Independent claim 96 of the subject application as amended is directed to a method of associating with a sample of genetic material one of a predetermined plurality of genotypic

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 23

classes defined with respect to a genetic locus sited in the genetic material together with a corresponding confidence measure, which includes a step of obtaining with respect to each of the genotypic classes corresponding reaction-value data-point conditional-probability-measure distribution information, which provides, over a set of hypothetical reaction-value data points, a conditional probability measure as a function of the reaction values of each hypothetical reaction-value data point given the genotypic class. The method of amended claim 96 includes the further step of evaluating for each of the genotypic classes the corresponding reaction-value data-point conditional-probability-measure distribution information with respect allele-indicative reaction values of the reaction-value data point corresponding to the sample, to obtain for each of the corresponding genotypic classes a reaction-value data-point conditional probability measure of the reaction-value data point, given the genotypic class.

Independent claim 106 of the subject application as amended is directed to a method of associating with a sample of genetic material from a subject (i) one of a predetermined plurality of genotypic classes defined with respect to a genetic locus sited in the genetic material and (ii) a confidence measure for the association of the genotypic class with the sample. The method of amended claim 106 includes the step of obtaining with respect to each of the genotypic classes corresponding reaction-value data-point conditional-probability-measure distribution information which provides, over a set of hypothetical reaction-value data points, a conditional probability measure as a function of the hypothetical reaction-value data point given the genotypic class. The method of amended claim 106 further includes the step of evaluating the reaction-value data-point conditional-probability-measure distribution information corresponding to a genotypic class associated with the sample with respect to the reaction-value data point corresponding to the sample to obtain a reaction-value data-point conditional probability measure of the reaction-value data point given the sample genotypic class and establishing a confidence measure for the association of the sample genotypic class with the sample using the reaction-value data-point conditional probability measure of the reaction-value data point given the sample genotypic class.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 24

For the reasons given above, it is submitted that the Kimpton *et al.* publication as of the effective filing date of the subject application would not have disclosed the subject matter of any of independent claims 75, 96, and 106 of the application as amended, and indeed that the publication would have led persons skilled in the art away from the subject matter of amended claims 75, 96, and 106.

We turn now to the hypothetical combination of the Kimpton *et al.* publication with the Ledwina *et al.* publication proposed in the Office Action of 18 March 2005. In connection with the rejection in the Office Action under 35 U.S.C. § 103(a) of claims 75 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 96 through 98 inclusive, 102, 106 through 109 inclusive, and 112 through 115 inclusive as amended, the concept of Hardy-Weinberg equilibria was used with respect to proposing the hypothetical combination of the Kimpton *et al.* publication with the Ledwina *et al.* publication.

In particular, it was asserted generally on pages 5 and 7 of the outstanding Office Action that the Kimpton *et al.* publication disclosed a method of determining the genotype at a locus within genetic material which used Hardy-Weinberg equilibria. As may be seen from the Griffiths *et al.* book excerpt identified above, Hardy-Weinberg equilibrium refers to the statistical distribution of genotypes associated with a given genetic locus over a population of individuals who are the offspring from a population of parents who respectively selected mates without regard to the genotype of the mate with respect to the locus. For example, in the case of a diallelic locus having a first allele denoted A with a frequency of p over the population of the parent generation and a second allele denoted a having a frequency $q = 1 - p$ over the parent-generation population, under Hardy-Weinberg equilibrium, the frequencies of the three resulting genotypes over the population of the offspring generation would be as follows: the AA homozygotes would have a frequency of p^2 ; the Aa heterozygotes would have a frequency of $2pq$; and the aa homozygotes would have a frequency of q^2 . If, in contrast to the random selection of mates vis-à-vis the genotypes associated with the genetic locus under discussion

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 25

posited for Hardy-Weinberg equilibrium, members of the parent generation tended to select mates on the basis of the selected mate's exhibiting a trait like their own which was genetically determined by the genotypes associated with the locus, the frequencies of the genotypes over the population of the offspring generation would tend to deviate from the frequencies specified by Hardy-Weinberg equilibrium.

Regarding Hardy-Weinberg equilibrium, the Kimpton *et al.* publication disclosed at page 17, left-hand-side column, lines 16 through 22 and middle column, lines 4 through 10 that allele frequencies for each of the fourteen genetic loci under investigation were determined from a minimum of 50 randomly selected individuals from each of three different populations: Caucasian, Afro-Caribbean, and Asian. Each of these locus/population data sets was tested for Hardy-Weinberg equilibrium using a "log likelihood-G test." Of the $3 \times 14 = 42$ locus/population data sets tested, only one data set was found to deviate from Hardy-Weinberg equilibrium. The Kimpton *et al.* publication did not discuss any consequences of finding Hardy-Weinberg equilibrium or of finding a deviation from such equilibrium with respect to the locus/population data sets, other than to note at page 20, right-hand-side column, lines 23 through 35 that the one case of deviation from Hardy-Weinberg equilibrium might have been due to sampling error. The Kimpton *et al.* publication did not disclose or suggest using the test for Hardy-Weinberg equilibrium in connection with determination of the genotype of any individual. Indeed, any test for Hardy-Weinberg equilibrium takes as input genotype-enumeration data based on genotype identifications which would have to have been made previously, as, it is submitted, persons of ordinary skill in the art would have appreciated as of the effective filing date of the subject application.

In the outstanding Office Action at the bottom of page 6, it was asserted that the Ledwina *et al.* publication disclosed a method by which genotypes could be determined. It is respectfully submitted that, on the contrary, the Ledwina *et al.* publication concerned a class of statistical tests applicable to genotype-enumeration data from a sample of N individuals whose genotypes

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 26

had been previously determined to provide a basis for accepting or rejecting the hypothesis that the frequencies of genotypes over the population from which the sample of individuals had been taken exhibited Hardy-Weinberg equilibrium. More particularly, the Ledwina *et al.* publication purported to derive criteria to determine if a given statistical test for accepting or rejecting the hypothesis of Hardy-Weinberg equilibrium among the genotypes of a population based on genotype-enumeration data from a sample of N individuals drawn from that population had statistical justification of a certain sort, which the publication referred to as being an “admissible” test. The particular test for which the greatest detail was provided in the Ledwina *et al.* publication was a so-called chi-square χ^2 goodness-of-fit test. No specific mention was made in the Ledwina *et al.* publication of the log likelihood-G test used in the Kimpton *et al.* publication to test for Hardy-Weinberg equilibrium in various locus/population data sets.

In the outstanding Office Action, with reference to an expression for a “conditional distribution of \mathbf{T} given $\mathbf{Z} = \mathbf{z}$ ” set out in lines 7 through 10 of page 163 of the Ledwina *et al.* publication, it was asserted that the publication disclosed establishing a distribution set of probability distributions, associating hypothetical values of a sort not specified in the Office Action with corresponding probabilities for each genotype of interest, and applying a first such unspecified value to each pertinent probability distribution assertedly to determine a measure of conditional probability of each genotype of interest. However, as defined in the first sentence of section 1 on page 161 of the Ledwina *et al.* publication and the respective first sentences of the first two paragraphs of section 2, the statistic \mathbf{T} was a random vector whose components specified, with respect to a particular genetic locus having a number m of alleles denoted A_i , the respective numbers of individuals in a sample of N individuals who had, for a first $m-1$ of the alleles, homozygous genotypes $A_i A_i$ or heterozygous genotypes $A_i A_j$, $i \neq j$, irrespective of whichever of the alleles A_i and A_j came from the mother or the father of the individual. The statistic \mathbf{T} thus could be regarded as an incomplete genotype-enumeration statistic; incomplete in the sense that only $m-1$ of the m alleles were accounted for directly. The statistic \mathbf{Z} was defined

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 27

to be a random vector whose components specified, with respect to the same genetic locus, the respective numbers of individuals in the sample of N individuals who had, for the first $m-1$ of the alleles, the allele A_i , with homozygous individuals having two copies of the allele A_i evidently being counted twice. The statistic \mathbf{Z} thus could be regarded as an incomplete allele-enumeration statistic. Consequently, contrary to the assertion in the Office Action, the expression for the conditional distribution of \mathbf{T} given $\mathbf{Z} = \mathbf{z}$ derived in the Ledwina *et al.* publication associated hypothetical vector values of the incomplete genotype-enumeration statistic \mathbf{T} , which had components which specified the respective numbers of individuals in a sample of N individuals who had genotypes $A_i A_j$, $1 \leq i, j \leq m-1$, irrespective of the parental source of the alleles A_i and A_j , with corresponding probabilities for each particular vector value \mathbf{z} of the incomplete allele-enumeration statistic \mathbf{Z} , which had components which specified the respective numbers of individuals in the sample of N individuals who had alleles A_i , $1 \leq i \leq m-1$. Significantly, for any particular sample of N individuals, the vector components of both the incomplete genotype-enumeration statistic $\mathbf{T} = \mathbf{t}$ and the incomplete allele-enumeration statistic $\mathbf{Z} = \mathbf{z}$ were formed in the Ledwina *et al.* publication from previously obtained complete genotype-enumeration data $\{x_{ij}\}$, $1 \leq i, j \leq m$, for the sample, as may be seen with respect to equations (1) and (2) on page 162 of the publication. Particular methods by which the genotypes could be identified to obtain the complete genotype-enumeration data $\{x_{ij}\}$ were irrelevant to the derivations of the Ledwina *et al.* publication and none was specified or suggested.

The expression in the Ledwina *et al.* publication referred to in the outstanding Office Action for the conditional distribution of the incomplete genotype-enumeration statistic \mathbf{T} given a particular value \mathbf{z} of the incomplete allele-enumeration statistic \mathbf{Z} for a sample of N individuals set out in lines 7 through 10 of page 163 of the publication evidently applied to such a sample whether the sample was taken from a population whose genotypic frequencies were in Hardy-Weinberg equilibrium or was taken from a population whose genotypic frequencies deviated from Hardy-Weinberg equilibrium to a greater or lesser extent. In lines 11 through 18 of page

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 28

163 of the publication, the general expression of lines 7 through 10 was reduced to the special case of an expression, denoted $P_{T|z,H}(t)$ for $T = t$, for the conditional distribution of T given $Z = z$ for a sample of N individuals in which the genotypic frequencies of the population from which the sample of individuals was taken were hypothesized to be in Hardy-Weinberg equilibrium. The expression $P_{T|z,H}(t)$ for the conditional distribution of the incomplete genotype-enumeration statistic T given a particular value z of the incomplete allele-enumeration statistic Z for a sample of N individuals to be tested and further given the hypothesis that the genotypic frequencies of the population from which the sample was taken were in Hardy-Weinberg equilibrium was used in the Ledwina *et al.* publication purportedly to derive a particular chi-square X^2 goodness-of-fit test which involved dividing all possible vector values t of the incomplete genotype-enumeration statistic T into two mutually exclusive classes: a hypothesis-acceptance class $\{t: X^2(t,z) < c_\alpha\}$ and a hypothesis-rejection class $\{t: X^2(t,z) \geq c_\alpha\}$, such that the overall probability that any vector value t possible for a sample of N individuals for which the vector value z was as determined for the particular sample to be tested fell in the hypothesis-rejection class and the hypothesis that the genotypic frequencies of the population from which the sample was taken were in Hardy-Weinberg equilibrium was true would be less than a selected "significance level" α . In particular, as noted on page 164, lines 4 through 7 of the Ledwina *et al.* publication, the constant c_α used in defining the hypothesis-acceptance and hypothesis-rejection classes for the chi-square X^2 test of the publication was determined by a procedure which involved summing the conditional distribution $P_{T|z,H}(s_i)$ evaluated at certain vector values $\{s_i\}$ of the incomplete genotype-enumeration statistic T possible for a sample of N individuals with respect to the m -allele genetic locus given the particular value z of the incomplete allele-enumeration statistic Z as determined for the particular sample to be tested. The vector values $\{s_i\}$ of the statistic T for which the conditional distribution $P_{T|z,H}(s_i)$ was summed to determine the constant c_α were those values $\{s_i\}$ having corresponding chi-square statistics $\{X^2(s_i,z)\}$ evaluated at such values which were the greatest in magnitude relative to the chi-square statistics evaluated at all other vector values of the statistic T possible for a sample of N individuals given the particular value z .

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 29

From the discussion set forth in the preceding paragraphs, it appears evident, it is respectfully submitted, that the assertion in the Office Action of 18 March 2005 that the Ledwina *et al.* publication disclosed establishing a distribution set of probability distributions, associating hypothetical values of an unspecified sort with corresponding probabilities for each genotype of interest, and applying a first such unspecified value to each pertinent probability distribution assertedly to determine a measure of conditional probability of each genotype of interest generally mischaracterized the disclosure of the publication, since, as persons of ordinary skill in the art as of the effective filing date of the subject application would have appreciated, the conditional probability distributions of the Ledwina *et al.* publication associated hypothetical vector values of an incomplete genotype-enumeration statistic \mathbf{T} , which had components which specified the respective numbers of individuals in a sample of N individuals who, with respect to a particular genetic locus having a number m of alleles denoted A_i , had genotypes $A_i A_j$, $1 \leq i, j \leq m-1$, irrespective of the parental source of the alleles A_i and A_j , with corresponding probabilities for each particular vector value \mathbf{z} of an incomplete allele-enumeration statistic \mathbf{Z} , which had components which specified the respective numbers of individuals in the sample of N individuals who had alleles A_i , $1 \leq i \leq m-1$. It is submitted that the Ledwina *et al.* publication neither disclosed or suggested using any test for Hardy-Weinberg equilibrium in connection with determination of the genotype of any individual, nor disclosed or suggested using any conditional distribution of \mathbf{T} given $\mathbf{Z} = \mathbf{z}$ for a sample of N individuals employed in the publication to characterize tests for Hardy-Weinberg equilibrium in connection with determination of any individual's genotype.

In the outstanding Office Action it was asserted that it would have been *prima facie* obvious to a person of ordinary skill in the art to modify the method of the Kimpton *et al.* publication to use the conditional probability distribution method of the Ledwina *et al.* publication assertedly since the Kimpton *et al.* publication disclosed the use of Hardy-Weinberg equilibria and since the Ledwina *et al.* publication referred to characterizing the class of

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 30

admissible tests for Hardy-Weinberg equilibrium in a multi allelic system. However, as noted above, neither the Kimpton *et al.* publication nor the Ledwina *et al.* publication disclosed or suggested using a test for Hardy-Weinberg equilibrium in connection with determination of the genotype of any individual. To the extent it might have occurred to a person of ordinary skill in the art to combine the disclosures of the Kimpton *et al.* publication and Ledwina *et al.* publication, we submit such a person would either have evaluated the log likelihood-G test reportedly used in the Kimpton *et al.* publication to test locus/population data sets for Hardy-Weinberg equilibria according to the admissibility criteria disclosed in the Ledwina *et al.* publication or would have substituted the particular chi-square X^2 goodness-of-fit test disclosed in the Ledwina *et al.* publication for the log likelihood-G test used in the Kimpton *et al.* publication. It is submitted that neither such hypothetical combination would have met the limitations of any of independent claims 75, 96, or 106 of the subject application as amended, nor would have suggested the claimed subject matter to a person of ordinary skill in the art as of the effective filing date of the application, since, as noted above, neither the Kimpton *et al.* publication nor Ledwina *et al.* publication disclosed a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at a locus within genetic material in connection with a method involving determining the genotype of a subject at the locus using a reaction value indicative of a given allele at the locus.

In the outstanding Office Action, it was asserted that the Jeanpierre publication would have motivated the hypothetical combination of the Kimpton *et al.* publication and the Ledwina *et al.* publication proposed in the Office Action. The Jeanpierre publication disclosed a method for deriving the probability for a genotype of an “unsampled” person based on genotype assignments of family members in the pedigree of the unsampled person. However, particular methods by which the genotypes could be assigned to family members who were sampled in the pedigree of the “unsampled” person, other than possibly direct observation of a genetic disease in such family members, were irrelevant to the derivations of the Jeanpierre publication and none

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 31

was specified or suggested. In particular, no mention was made in the Jeanpierre publication of a reaction value indicative of the presence of a given allele at a genetic locus, let alone of a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at a locus within genetic material in connection with a method involving determining the genotype of a subject at the locus using a reaction value indicative of a given allele at the locus. The Jeanpierre publication thus does not cure the infirmities of the Kimpton *et al.* publication and the Ledwina *et al.* publication as references against the claims of the subject application.

Each of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication is concerned with a different and disparate sort of genetic analysis: determination of a DNA profile of an individual from a sample of the individual's DNA in the case of the Kimpton *et al.* publication, whether the distribution of genotypes previously determined for a sample of N individuals drawn from a population of multiallelic diploid individuals supports in a statistically-valid sense the hypothesis that the population exhibits a Hardy-Weinberg equilibrium state in the case of the Ledwina *et al.* publication, and evaluation of the probability of the genotype of an individual whose genetic material is not available for testing from the genotypes of family members in the pedigree of the individual in the case of the Jeanpierre publication. It is submitted that in view of the fundamentally different sorts of genetic analysis disclosed in the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication, it would never have occurred to a person of ordinary skill in the art as of the effective filing date of the subject application to combine these three publications as proposed in the outstanding Office Action.

In the Office Action of 18 March 2005, it was asserted that the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication were in the same field of endeavor; namely, genotypic analysis, and that each of the publications was assertedly pertinent to the problem of analysis of genotypes.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 32

Whatever may have been the understanding of persons of ordinary skill in the art as of the effective filing date of the subject application with respect to the breadth and boundaries of the expression “genotypic analysis,” it is submitted that such persons would have appreciated that the differences among the disclosures of the three publications were fundamental. As discussed above, the Kimpton *et al.* publication disclosed a method for determining the genotype profile of an individual with respect to fourteen specially selected short-tandem-repeat loci employing genetic material taken from the individual and amplified by PCR and an analysis of whether such genotype profiles could be used to distinguish different members of a population; the Ledwina *et al.* publication disclosed a statistical analysis of inferences which could be drawn about the relative numbers of different genotypes in a population of many individuals based on the relative numbers of previously-determined genotypes in a group of individuals selected randomly from the larger population; and the Jeanpierre publication disclosed a method of calculating the probability of a genotype for an individual for whom genetic material for direct analysis was unavailable based on previously-determined genotypes of family members. It is submitted that, in view of the fundamental differences among the disclosures of the three publications, a person of ordinary skill in the art as of the effective filing date of the subject application would not have attempted the hindsight hypothetical combination the disclosures of the publications proposed in the outstanding Office Action.

That persons of ordinary skill in the art recognized fundamental distinctions between different subfields of the field of genetic analysis is evident from the following passage from the book *An Introduction to Genetic Analysis, Fifth Edition*, by Griffiths *et al.* cited above at page 738, column 1, lines 1 through 15 and made of record in an information disclosure statement filed with respect to the subject application on 8 April 2004:

Mendel’s investigations of heredity — indeed all the interest in heredity in the nineteenth century — arose from two related problems: how to breed improved crops and how to understand the nature and origin of species. What is common to these problems (and differentiates them from the problems of transmission and

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 33

gene action) is that they are concerned with *populations* rather than with *individuals*. Studies of gene replication, protein synthesis, development, and chromosome movement focus on processes that go on within cells of individual organisms. But transformation of a species, either in the natural course of evolution or by deliberate intervention of human beings, is a change in the properties of a collectivity — of an entire population or a set of populations. [Italics in original.]

Assuming for the sake of argument only that it might have occurred to a person of ordinary skill in the art as of the effective filing date of the application to attempt to combine the respective disclosures of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication, it is submitted that any resulting hypothetical combination would not have met the limitations of any of independent claims 75, 96, and 106 of the subject application as amended, since, for example, not one of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication disclosed or suggested a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at a locus within genetic material in connection with a method involving determining the genotype of a subject at the locus using a reaction value indicative of a given allele at the locus.

For the reasons set forth above, it is submitted that the Kimpton *et al.* publication considered alone or in any combination with the Ledwina *et al.* publication and/or the Jeanpierre publication would not have disclosed or suggested the method of any of independent claims 75, 96, and 106 of the subject application as amended to a person of ordinary skill in the art as of the effective filing date of the application. The rejection under 35 U.S.C. § 103(a) of amended independent claims 75, 96, and 106 as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as motivated in view of the Jeanpierre publication is without justification, it is submitted, and should be withdrawn.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 34

Each of claims 76 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 97, 98, 102, 107 through 109 inclusive, and 112 through 115 inclusive respectively depends directly or indirectly on one of independent claims 75, 96, and 106 as amended and consequently incorporates the limitations of one of amended independent claims 75, 96, and 106 by reference. The reasoning set forth above concerning distinctions between the Kimpton *et al.* publication considered alone or in combination with the Ledwina *et al.* publication or the Jeanpierre publication and the method of any of independent claims 75, 96, and 106 as amended therefore applies with equal force with respect to dependent claims 76 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 97, 98, 102, 107 through 109 inclusive, and 112 through 115 inclusive. Consequently, it is submitted that the Kimpton *et al.* publication considered alone or in any combination with the Ledwina *et al.* publication and/or the Jeanpierre publication would have neither disclosed nor in any way suggested the subject matter of claims 76 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 97, 98, 102, 107 through 109 inclusive, and 112 through 115 inclusive to a person of ordinary skill in the art as of the effective filing date of the subject application. It is submitted, therefore, that the rejection under 35 U.S.C. § 103 of dependent claims 76 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 97, 98, 102, 107 through 109 inclusive, and 112 through 115 inclusive of the subject application as amended as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as motivated in view of the Jeanpierre publication is without justification and should be withdrawn.

In sum, for the reasons set forth above, it is submitted that the rejection under 35 U.S.C. § 103(a) of claims 75 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 96 through 98 inclusive, 102, 106 through 109 inclusive, and 112 through 115 inclusive of the subject application as amended as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as motivated in view of the Jeanpierre publication is unwarranted and should be withdrawn.

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 35

E.2 The Kimpton *et al.* Publication in View of
the Ledwina *et al.* Publication as Motivated
in View of the Jeanpierre Publication and
Further in View of the Goelet *et al.* '712
Published International Application

As disclosed in the abstract, the Goelet *et al.* '712 published international application disclosed a method for determining the identity of a nucleotide base at a specific position in a nucleic acid of interest and a method for determining the presence or absence of a particular nucleotide sequence in a sample of nucleic acids. The methods entailed contacting nucleic acid of interest with an oligonucleotide primer under hybridizing conditions and treating the resulting duplex, if any, with a terminator reagent under conditions permitting base pairing of a complementary terminator present in the reagent and the occurrence of a template-dependent, primer extension reaction so as to incorporate the terminator at the 3' end of the primer. The identity of the terminator at the 3' end of the primer determined whether the hybridization occurred and the identity of the base complementary to the terminator.

The Kimpton *et al.* publication disclosed an automated DNA profiling method which employed three multiplex groups of specially selected three to five-base pair short-tandem-repeat loci which were amplified groupwise by PCR and analyzed by denaturing polyacrylamide sequencing gels.

The Goelet *et al.* published application does not connect the disparate methodologies of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication. For the reasons discussed in the preceding subsection E.1, it is submitted that it would not have occurred to a person of ordinary skill in the art, as of the effective filing date of the subject application, to combine the disparate methods of the Kimpton *et al.* publication and the Ledwina *et al.* publication, with or without the motivation of the Jeanpierre publication, in any combination with each other or with the Goelet *et al.* published application. Moreover, assuming for the sake of argument only that it might have occurred to a person of ordinary skill in the art as

Applicants: Stephen E. Lincoln and
Michael R. Knapp
Serial No.: 09/618,178
Filed: 18 July 2000
Page 36

of the effective filing date of the application to attempt to combine the respective disclosures of the Kimpton *et al.* publication, the Ledwina *et al.* publication, the Jeanpierre publication, and the Goelet *et al.* published application, any such hypothetical attempted combination would not have met the limitations of any independent claims 75, 96, and 106 of the subject application as amended for the reasons discussed in the preceding subsection E.1, nor of any of dependent claims 76 through 82 inclusive, 85 through 87 inclusive, 91 through 95 inclusive, 97, 98, 100, 102, and 107 through 115 inclusive, each of which respectively depends on one of independent claims 75, 96, and 106 directly or indirectly. It is submitted that the rejection of claims 75 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, 100, 102, and 106 through 115 inclusive of the subject application as amended under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication, in view of the Ledwina *et al.* publication, as motivated in view of the Jeanpierre publication, and further in view of the Goelet *et al.* '712 published international application is unwarranted and should be withdrawn.

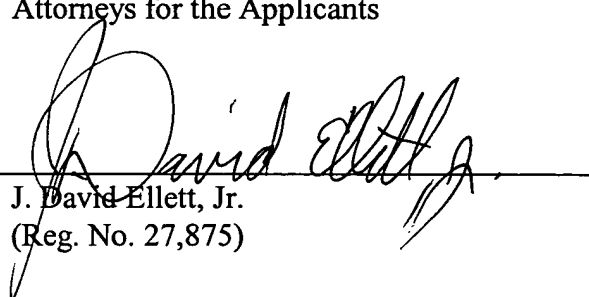
F. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

Attorneys for the Applicants

by:


J. David Ellett, Jr.
(Reg. No. 27,875)

Telephone No. (212) 813-1600